Journal of the American College of Cardiology
© 1999 by the American College of Cardiology
Published by Elsevier Science Inc.

Vol. 34, No. 3, 1999
ISSN 0735-1097/99/$20.00
PII S0735-1097(99)00301-0

EDITORIAL COMMENT

Elevation of Creatine Kinase, MB Fraction After Elective Coronary Intervention: A Valid Surrogate End Point of Poor Late Outcome?*

Guy S. Reeder, MD
Rochester, Minnesota

Over the last decade, a substantial body of evidence that is predominately observational and usually associated with the evaluation of new devices and drugs has characterized the circumstances and outcomes of periprocedural elevation of creatine kinase, MB fraction (CK-MB). Most, but not all, studies could be summarized as follows:

- Release of CK-MB is common if sought for in up to 25% of cases of percutaneous intervention; most commonly <5 times the upper limit of normal.
- The causes may include angiographically evident events, such as branch vessel occlusion or embolization, but just as often they may be neither symptomatic or angiographically apparent.
- The likelihood of enzyme release is greater with nonballoon devices, such as rotablator, directional atherectomy and stents.
- Enzyme release is correlated with late mortality in some studies.
- The exact level of enzyme elevation to diagnose "myocardial infarction" with its attendant clinical and economic implications for patient management is uncertain, although an upper level of three times normal has been suggested (1).

In this issue of the *Journal*, Kini et al. (2) found CK-MB elevation in nearly 19% of 1,675 patients undergoing elective percutaneous coronary intervention. A procedural cause was identifiable in less than one-half of the patients. During the mean follow-up of 13 ± 3 months, there was only a nonsignificant trend (1.6% vs. 1.3%) in increased mortality for all patients with CK-MB elevation, and no adverse in-hospital events in those with <5 times normal elevation. On multivariate analysis, predictors of CK-MB elevation included severity of coronary and systemic atherosclerosis, stenting and absence of beta-adrenergic blocking agent therapy.

See page 663

A recently reported preliminary analysis of over 7,000 consecutive elective percutaneous interventions showed similar findings, with only a weak trend toward worse outcome with <5 times normal enzyme elevations, but there was a high association between late mortality and other comorbidities by multivariate analysis (3). These findings emphasize two critical issues that remain controversial:

- At what enzyme level should a diagnosis of "periprocedural myocardial infarction" be made?
- Are modest elevations (<5 times normal) of CK-MB simply a correlate (i.e., a surrogate marker related to the extent of disease) (4) or are they somehow causative of subsequent adverse events, including mortality?

Traditionally defined myocardial infarction usually evolves from an occluded artery, resulting in left ventricular dysfunction, the extent of which is a strong predictor of postinfarct survival, and recurrent events, including mortality, occur relatively early, often in one to two months after infarction. The cardiac enzyme elevations of <5 times normal, which most commonly occur after percutaneous coronary intervention, are often not associated with an occluded vessel, do not produce significant left ventricular dysfunction and have usually been associated (in positive studies) with late mortality (5). The mechanism of late death has not been defined. It has been suggested that "microinfarcts," which manifest as enzyme release during percutaneous coronary interventions, might predispose to late arrhythmic events. This is highly unlikely, given the large body of evidence showing that malignant ventricular arrhythmias are predominantly confined to patients with a large infarction, substantial left ventricular systolic dysfunction (ejection fraction <40%), left ventricular enlargement and postinfarct remodeling. If enzyme release is causally related to late mortality, a reduction in enzyme release should reduce mortality. However, the substantial reduction in periprocedural CK-MB elevation by glycoprotein IIb/IIIa platelet receptor antagonists has generally resulted in only a nonsignificant trend toward reduced mortality, suggesting that enzyme elevation is correlated with but may not be causative of late outcome, at least at modest levels. In a meta-analysis of 16 randomized, controlled trials of glycoprotein IIb/IIIa agents in over 32,000 patients, no significant mortality difference at 30 days or 6 months could be documented (6). (Only one trial, EPISTENT, preliminarily reported at the February 1999 meeting of the American College of Cardiology (7), showed a 1% absolute mortality

*Editorials published in the *Journal of the American College of Cardiology* reflect the views of the authors and do not necessarily represent the views of *JACC* or the American College of Cardiology.

From the Mayo Clinic/Foundation, Rochester, Minnesota.

reduction for the combination of abciximab and stenting vs. stenting alone. There was no mortality reduction from abciximab, however, in nonstented patients.)

The study by Kini et al. (2) adds to the controversy regarding periprocedural CK-MB elevation and subsequent coronary events. What are the clinical implications of this report? One may hypothesize that the limits for dismissal of patients with elevated periprocedural CK-MB may be extended to five times normal in the absence of high risk clinical factors. Prospective validation of this hypothesis will be needed. Further studies are also needed to establish the mechanism of death in those investigations that have shown a correlation between mortality and modest elevation of CK-MB. All patients, especially those with enzyme elevation, should have long-term risk reduction with agents proven to prolong survival in coronary artery disease: aspirin, beta-blockers, angiotensin-converting enzyme inhibitors and statins. Longer follow-up periods of studies correlating CK-MB release with mortality are warranted.

Reprint requests and correspondence: Dr. Guy S. Reeder, Mayo Clinic/Foundation, 200 First Street SW, Rochester, Minnesota 55905.

REFERENCES

1. Califf RM, Abdelmeguid AE, Kuntz RE, et al. Myonecrosis after revascularization procedures. J Am Coll Cardiol 1998;31:241–51.
2. Kini A, Marmur JD, Kini S, et al. Creatine kinase-MB elevation after coronary intervention correlates with diffuse atherosclerosis, and low-to-medium level elevation has a benign clinical course: implications for early discharge after coronary intervention. J Am Coll Cardiol 1999;34:663–71.
3. Stone GW, Mehran R, Lansky AJ, et al. Long-term influence of CPK-MB elevation on mortality after percutaneous intervention—analysis of 7,359 patients (abstr). J Am Coll Cardiol 1999;33 Suppl:80A.
4. Fleming TR, DeMets DL. Surrogate end points in clinical trials: are we being misled? Ann Intern Med 1996;125:605–13.
5. Topol EJ, Ferguson JJ, Weisman HF, et al., for the EPIC Investigator Group. Long-term protection from myocardial ischemic events in a randomized trial of brief integrin β_3 blockade with percutaneous coronary intervention. JAMA 1997;278:479–84.
6. Kong DF, Califf RM, Miller DP, et al. Clinical outcomes of the therapeutic agents that block the platelet glycoprotein IIb/IIIa integrin in ischemic heart disease. Circulation 1998;98:2829–35.
7. Topol EJ. Presented at the 48th Annual Scientific Session of the American College of Cardiology, March 7–10, 1999.